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Unipolar Depression and the Progression of Coronary Artery Disease: Toward an Integrative Model

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Key Words

Depression, symptom dimensions • Coronary artery disease • Myocardial infarction • Atherosclerosis

Abstract

Background: Despite extensive research on the relationship between depression and coronary artery disease (CAD) after an acute coronary syndrome (ACS), causal interpretations are still difficult. This uncertainty has led to much confusion regarding screening and treatment for depression in CAD patients. **Method:** A critical and conceptual analysis of the pertinent literature, which elaborates the implications of the heterogeneity in symptom pattern, etiology, and course of depression in CAD patients. **Results:** We propose an integrative dynamic model of the depression-CAD relationship. The model rests on three core hypotheses: (1) Depression in CAD patients consists of mixtures of two types of depression, denoted as ‘cognitive/affective’ and ‘somatic’ depression, each having a somewhat characteristic symptom expression and etiology. (2) Effects of depression on CAD depend on the type and duration of depression. The dynamic aspect of the model indicates that post-ACS depression shifts, when it persists, from a marker of the severity (somatic type) and

meaning (cognitive/affective type) of the ACS to a largely indirect causal factor in the progression of CAD. (3) The most plausible pathways mediating the effects of persistent/recurrent depression, irrespective of type, on cardiac prognosis are behavioral and act by making depressed CAD patients more susceptible to other CAD risks. The model offers testable predictions and explanations for a variety of apparently unrelated or inconsistent findings. **Conclusion:** The proposed model may have potential for integrating findings regarding the depression-CAD relationship, contributing to the clarification of discords on screening and treatment of depression, and guiding future research.

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Introduction

Despite extensive research on the association between depression and the development and progression of coronary artery disease (CAD), the causal significance of the relationship remains unclear. Recent publications in top medical and psychiatric journals [1–5] show that this uncertainty has contributed to confusion over the usefulness of screening and optimal treatment for depression in

CAD patients. Because CAD and depression will soon carry the largest burden of disease, understanding their relationship is more important than ever.

Research has implicated depressive disorder as both an etiologic and prognostic risk factor in CAD. Studies of depression in the context of CAD typically include the DSM-IV categories of major depressive disorder, minor depression, dysthymic disorder, and depressive disorder not otherwise specified. Reviews of *etiologic* studies that look for signs of CAD in healthy depressed and non-depressed individuals conclude that depression is an independent (i.e., causal) risk factor in CAD development [6–11]. But some authors point out that few studies have controlled for possible subclinical atherosclerosis, e.g. Stewart et al. [12].

Reviews of nearly three dozen *prognostic* studies show less consensus. These studies typically follow CAD patients with a recent acute coronary syndrome (ACS) to monitor the course of the disease, with mortality or CAD events as outcomes [9, 10, 13–16]. Most reviews conclude that depression is a risk factor for CAD prognosis. But some have questioned the causal interpretation [10, 15] or arrived at an undecided position [16]. In addition, knowledge about depression and CAD is largely derived from studies in developed countries. The results from the international INTERHEART study and, to a lesser extent, the World Mental Health Surveys suggest substantial cross-cultural consistency in associations [17, 18].

The critique of a causal interpretation is threefold [10, 15, 19, 20]: (1) insufficient adjustment for accurately measured plausible confounders, in particular the severity of atherosclerosis and ACS, (2) reverse causality (i.e., it is the atherosclerosis or ACS that leads to depression), and (3) negative or inconclusive findings of randomized controlled trials on the effects of depression treatment on cardiac prognosis in post-ACS patients [21–23]. To date, no study using randomized comparisons has found a decreased cardiovascular risk in post-ACS patients treated with antidepressants or psychotherapy. Some researchers have suggested cardiac benefits for patients receiving or responding to antidepressive treatment [24–28], but these findings are based on nonrandomized comparisons. New empirical studies continue to find significant etiologic [29, 30] and prognostic [31, 32] associations between depression and CAD. But these findings have not silenced the doubts.

This paper integrates available evidence to formulate a model of the relationship between post-ACS depression and the progression of CAD. The model rests on

three key hypotheses [33–35]. The first hypothesis is that depression comorbid with CAD is a mixture of two prototypical types of depression: ‘cognitive/affective’ and ‘somatic/affective’. The second hypothesis posits that the nature and course of the depression affects its relationship with CAD progression. The third hypothesis argues that behavioral mediations best explain the effects of depression on cardiac prognosis – with depressed CAD patients being more susceptible to other CAD risks.

We first explore the assumptions and present supportive and conflictive evidence. Next, we derive some testable predictions from the model and discuss how it accommodates and integrates apparently inconsistent and puzzling findings. Finally, we discuss its relevance for screening, treatment, and future research. Despite some supportive evidence, the three key hypotheses proposed clearly need further testing.

Post-Myocardial Infarction Depressions Are Mixtures of ‘Cognitive/Affective’ and ‘Somatic/Affective’ Depressions

Depression is a highly heterogeneous syndrome characterized by at least 2 weeks of depressed mood and/or loss of interest and a number of associated symptoms. DSM-IV major depression requires the presence of 5 out of 9 symptoms. The heterogeneity is clearly shown by the strongly varying patterns of relationships of these 9 symptoms with all kinds of validators including personality, demographics, clinical and prognostic characteristics [36]. Refining the diagnostic category of depression is generally seen as highly relevant and extremely challenging. Historically, many have attempted to type depression in terms of symptom pattern and etiology. Important distinctions of depression in the DSM-IV involve severity, duration, recurrence, melancholic and atypical features, and a residual category of depressive disorder not otherwise specified. Lichtenberg and Belmaker [37] recently distinguished 10 types of depression, arguing that subtyping will improve treatment effectiveness.

Latent class methods often show multiple classes that differ in severity and core symptoms (typical versus atypical) [38]. A recent study of 818 persons with a DSM-IV diagnosis of current depression identified three classes in the 16 depressive symptoms from the Composite International Diagnostic Interview: severe melancholic, severe atypical, and moderately severe depressions [39]. Factor-

Fig. 1. Prototypical etiology of the cognitive/affective and somatic subtypes of depression in ACS patients. ANS = Autonomus nervous system.

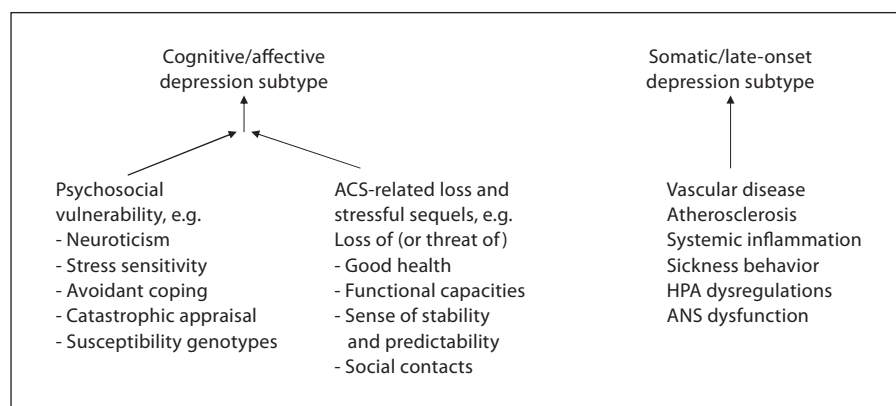


Table 1. Prototypical symptoms of the cognitive/affective and somatic/affective dimensions of depression

<i>Cognitive/affective subtype</i>
Depressed mood
Lack of interest
Suicidal thoughts
Negative feelings/cognitions about self
Self-dislike
Sense of failure
Self-accusations
Self-criticism and blame
Guilt
Interpersonal sensitivity
Future pessimism
<i>Somatic/affective subtype</i>
Fatigability
Psychomotor agitation/retardation
Work difficulty
Sleep problems (mostly more sleep)
Aches and pains
Appetite disturbance (mostly increased appetite)
Weight disturbance (mostly weight gain)
Depressed mood
Data based on multiple studies [12, 39, 41–48].

analytic and item response methods to type depression symptoms commonly suggest three-dimensional structures, including ‘cognition/mood’ and ‘arousal/somatic’ [36, 40, 41].

Cognitive/Affective versus Somatic/Affective Symptoms

Similar dimensions found in depressed CAD and ACS patients are usually labeled as ‘cognitive/affective’ versus

‘somatic/affective’ [12, 42–48]. Their prototypical symptoms are listed in table 1. Nearly all studies report that the somatic/affective dimension is associated with a less favorable cardiac prognosis. Most measured depression with BDI- or DSM-IV-based self-report measures, such as the Patient Health Questionnaire.

Not all evidence supports the notion of these prototypes. Using advanced psychometrics, Doyle et al. [49] showed that common somatic depression symptoms (e.g., fatigue) and less-common cognitive depression symptoms (e.g., hopelessness) form a strong one-dimensional scale, ordered in a hierarchy reflecting their prevalence. However, the only somatic items measured were fatigue and exhaustion; symptoms regarding appetite, weight, and retardation/agitation were not included.

Somatic/affective depression shares symptoms with atypical depression as defined by DSM-IV. Recent studies suggest that the symptoms driving atypical depression may be more related to somatic or metabolic conditions than interpersonal sensitivity and mood reactivity, with appetite and weight increase possibly playing a key role [39, 50]. Therefore, the overlap between somatic/affective depression and atypical depression may even be larger.

The two prototypes of post-ACS depression are associated with distinct characteristics, pointing at partially different etiologies (fig. 1) [51–53]. Because post-ACS depression etiology was examined without distinguishing the two prototypes, the evidence is limited and largely indirect.

Etiology of ‘Typical Depression’

The etiology of typical depression is characterized by a combination of vulnerability and stressful life events, in particular loss of affection, skill or capacity, status, self-esteem, cherished belief, or the threat of such losses [54–

58]. As with other disease events, experiencing an ACS may involve loss of belief in one's good health, uncertainty about the future, (expected) functional impairments, and loss of social contacts [59–61]. The vulnerability consists of personality characteristics in the domains of neuroticism and stress sensitivity [56, 62, 63], avoidant and catastrophizing appraisal and coping tendencies [64, 65], and particular genotypes [66]. Loss-provoked depressions have symptom profiles that are marked by high levels of sadness, anhedonia, and guilt [67].

Etiology of 'Somatic Depression'

The etiology of somatic/affective depression is not known. One reason is the lack of a clear distinction between DSM-IV atypical depression, vascular depression [68, 69], late-onset depression [70, 71], somatic/affective post-ACS depression [42, 46, 47], vital exhaustion syndrome [72], and the neurovegetative symptom cluster [73, 74]. For ease of communication, we denote this family of depression types collectively as somatic depression. Major etiological pathways are postulated to be the presence of vascular disease, systemic inflammation and atherosclerosis [68, 73, 75–78]. High levels of pro-inflammatory cytokines and other immune signals – especially interleukin-1 and -6, tumor necrosis factor, C-reactive protein may induce sickness behavior [75–77, 79] and vital exhaustion [29, 80, 81], which both produce many symptoms of somatic depression. Deregulated hypothalamic pituitary-adrenal axis functioning (hyper- or hypocortisolemia) may also be involved in the etiology of somatic depression, although its role is less clear [82]. Other studies link autonomic nervous system dysfunction to somatic depression [83–85]. Of interest, a reanalysis of data from the Heart and Soul Study showed that somatic symptoms of depression were associated with reduced heart rate variability, whereas cognitive symptoms and overall depression were not [27]. Finally, disturbed central serotonin transmission has been associated with hypothalamic abnormalities that may contribute to altered appetite and decreased libido, and thalamic and brainstem dysregulations are thought to contribute to altered sleep [86].

Although suggestive, the evidence on the etiology of somatic depression is not consistent. For instance, the Heart and Soul Study found lower levels of C-reactive protein, fibrinogen, and interleukin-6 in depressed CAD patients [87]. A consistent but regularly ignored finding is that inflammation and atherosclerosis are found only in a subset of depressions [88], typically late-onset depressions [89, 90].

Different Courses

The course of ACS-triggered cognitive/affective symptoms is, we hypothesize, usually favorable, unless psychological vulnerabilities and disabilities are marked. Patients with no history of major depression and with a stable condition free from serious complications or severe impairment tend to adapt to chronic illness, and their depression resolves accordingly [91, 92]. CAD-associated somatic depressions are likely to persist because the ongoing CAD and underlying atherosclerosis and systemic inflammation will continue to fuel the etiology. Consequently, we hypothesize that the course of somatic depression as related to CAD will be less favorable than the cognitive/affective symptom cluster – unless the underlying physiological causes change for the better.

Continuous Transitions between Prototypes

Any mixture of cognitive/affective and somatic depression may develop in a particular individual with (subclinical) CAD. Both clusters may be present at the same time, especially after a major ACS having simultaneous psychological and physical impact. Also, the case mix of cognitive/affective and somatic depression may differ considerably among patient samples depending on the prevalence and severity of CAD and other atherosclerotic-related chronic physical conditions.

Effects of Depression on CAD Depend on Type and Duration

The second hypothesis posits that the effects of depression on CAD prognosis depend on type and course of depression. Duration is important because influences on behavioral and other pathways accumulate with time. We propose several predictions (table 2).

(1) Brief cognitive/affective depression is at most only weakly associated with CAD prognosis because the psychological meaning of the ACS probably depends somewhat on the biomedical severity of the ACS. Since the CAD prognosis also depends on ACS severity (the confounder), some causally spurious statistical association between cognitive/affective depression and CAD prognosis may result.

(2) In contrast, brief somatic depression is more strongly associated with CAD prognosis, due to confounding effects of ACS severity and underlying CAD, atherosclerosis, and associated physiological abnormalities (e.g., inflammation, endothelial dysfunction). These

Table 2. Strength and nature of association between post-ACS depression and CAD prognosis by type and duration of depression

Type of depression	Duration of depression	
	brief (remission within 6 months)	persistent (chronic/recurrent)
Cognitive-affective	none or weak association (noncausal) due to the weak association between severity of ACS and CAD and their psychological meaning	significant association due to accumulating negative effects on health behavior
Somatic	substantial but largely spurious association, due to confounding influences by severity of CAD and underlying atherosclerosis	strong association due to ongoing confounding plus accumulating negative effects on health behavior

physical factors may be involved in both somatic depression and CAD prognosis. Consequently, we hypothesize that the association of brief somatic depression with CAD prognosis is (largely) spurious. Evidence that nonadjusted risks of depression substantially decrease when adjusted for the ACS and CAD supports these predictions [10, 16, 93, 94].

(3) If persistent, we expect both types of depression to be associated with CAD prognosis, with the somatic link being stronger. The more persistent or recurrent the course of either type of depression, the more negative effects of persistent depression accumulate – making both types relevant for CAD prognosis (see hypothesis 3 below) [17, 24, 95–97]. Thus, when post-ACS depression persists, it shifts slowly from a marker of the severity (somatic type) and meaning (cognitive/affective type) of the CAD to a contributing factor in the progression of CAD.

Research has not yet examined the independent effects of type and duration on CAD prognosis, so we have no direct evidence related to these predictions. But they appear to be indirectly supported by the less favorable cardiac prognosis typically found only for somatic symptoms [12, 42, 43, 46]. In addition, depression persistence and/or treatment resistance are associated with longer episode duration [98, 99] and a poor CAD prognosis [2, 27]. Finally, the longer-term effects of depression on CAD are mediated by chronic/recurrent depression [100].

Significance of Behavioral Pathways in the Effects of Depression on CAD Prognosis

The third hypothesis addresses the pathways through which depression influences CAD prognosis. Regardless of type, plausible pathways mediating the effects of *per-*

sistent/recurrent depression on cardiac prognosis seem to be behavioral and thus indirect by making depressed CAD patients more susceptible to other CAD risks. Among these risks are nonoptimal CAD treatment [101], nonadherence to CAD treatment [102] and rehabilitation programs [103], and unhealthy lifestyle, including smoking, poor diet, and limited physical activity [104]. The consequences of the interplay between cognitive/affective and somatic symptoms and behavioral pathways may be substantial. Symptoms such as anhedonia, hopelessness, lethargy, and psychomotor slowing may promote decreased physical activity, lower treatment adherence, overeating.

The limited evidence available clearly supports a role for behavioral pathways. For example, Druss et al. [101] used medical charts and administrative files to compare the health care utilization of post-myocardial infarction patients with and without mental disorders. Patients with diagnosed affective disorder were significantly less likely to undergo cardiovascular procedures. Differences in medical (co)morbidity did not explain the lower rate of cardiovascular procedures in these patients.

In addition, depressed post-ACS patients have exhibited higher rates of nonadherence and dropout in CAD treatment regimens and cardiac rehabilitation [103, 105]. An important and effective component of rehabilitation programs is physical exercise, which also seems to have beneficial effects on depression [106, 107]. Behavioral activation is regarded as an effective way to promote physical exercise and improve depressive symptoms [108]. The strongest evidence to date comes from the Heart and Soul Study of stable CAD patients [104]. Lifestyle factors, in particular physical activity, accounted for almost 50% of the association between depression and new cardiac events. In contrast, physiological factors were unrelated to or only minimally associated with new cardiac events.

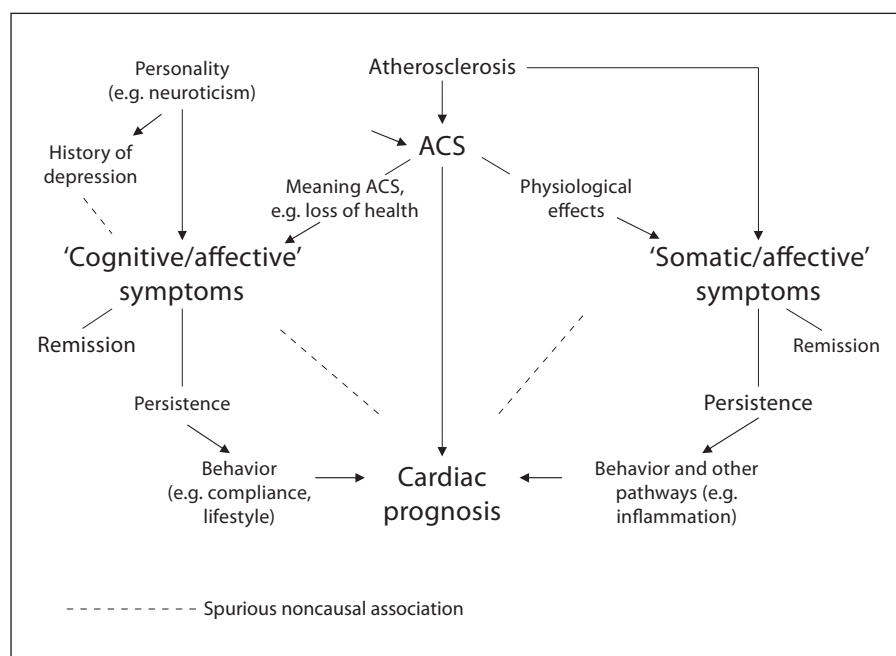


Fig. 2. Schematic overview of the relationships between depression and the prognosis of CAD.

Integrative Model of the Depression-CAD Relationship

Figure 2 summarizes the integrative model of the depression-CAD relationship. The model posits effects of depression on CAD and ACS outcomes as well as effects of CAD and ACS on depression. In both relationships, the effects depend on type and duration. The model hypothesizes that CAD, with its underlying atherosclerosis, is a risk factor for somatic depression but less so for cognitive/affektive depression. The reverse holds for ACS and initial CAD diagnosis. Atherosclerosis usually takes decades before causing clinical symptoms, so it may affect the risk of somatic depression long before the cardiologist diagnoses CAD.

Recently, the potential role of atherosclerosis in the dynamic bidirectional relationship between depression and CAD has been emphasized [2, 88, 109, 110]. Atherosclerosis-related systemic inflammation is probably involved in the etiology of somatic depression, while depression may affect the atherosclerotic process via its influence on CAD risks of smoking, diet, physical activity, and treatment adherence. Taken together, this leads to a complex cause-and-effect relationship that may be best described as a dynamic spiral of reciprocal influences [111], unfolding on a time scale of decades [75, 110].

Some Limitations

The model does not currently account for depression having symptomatic overlap and lifetime and concurrent comorbidity with anxiety disorders. Few studies have examined the relationship between anxiety and CAD, and most did not assess diagnosis [11]. Recent work suggests that both anxiety symptoms and generalized anxiety disorder are associated with the presence of CAD and an increased risk of adverse cardiac events in patients with stable CAD [32, 112]. The model does not imply that the depressive types in ACS patients are unrelated to anxiety disorder, but we cannot exclude the possibility that anxiety is driving the association. A related point is neuroticism, which is common to most anxiety and depressive disorders and associated with an increased risk of somatic symptoms [11].

How the Theory Integrates Apparently Inconsistent and Unrelated Findings

The model explains some apparently unrelated or inconsistent findings.

First, large randomized controlled trials of standard depression treatment such as antidepressants and cognitive behavioral therapy in recent-ACS patients have not successfully alleviated depressive symptoms and thus

could not determine whether effective treatment of depression improves CAD prognosis [21, 23, 113]. According to the model, this lack of effect may be due to the preponderance of somatic depression (typically resistant to standard depression treatments) in the case mix and the lack of cardiotoxicity of cognitive/affective depression of relatively brief duration. The proportion of treatment-responsive cognitive/affective depressions of long duration (and therefore slowly becoming cardiotoxic) in the case mix was probably too small or the improvement too minimal to have a significant effect on CAD prognosis.

Second, secondary analyses of clinical trials of depression in ACS patients identify two subgroups of patients with high cardiac risk: (i) those with unsuccessfully treated depression and (ii) those with high severity of depression soon after admission for ACS [2, 24, 27, 114; Frasure-Smith, personal commun., reported in 25]. The proposed model is consistent in asserting that most treatment-resistant depressions consist of somatic depressions. The reason these depressions do not respond well to standard depression treatments is probably their physiological CAD-related etiology. In addition, treatment resistance is associated with longer episode duration [98, 99], which fuels accumulation of behavioral risks, and, in turn, worsens CAD prognosis. This accumulation applies to both depression types, if persistent. Notably, the second finding – which links ACS-related depression severity with CAD prognosis – may be due to confounding by the severity of the ACS, underlying atherosclerosis, and associated inflammation.

Third, analyses by Glassman et al. [2, 115] demonstrate that certain subgroups of depressed CAD patients may benefit from antidepressant medication (sertraline, citalopram): those whose current depression episode began before the ACS, those with a history of depression, and those with the most severe episodes. Others have reported somewhat similar findings [3, 26, 114]. According to the model, these findings make sense if cognitive/affective symptoms characterize most episodes in these subgroups. This is plausible given the response to standard depression treatment and the history and pre-ACS onset of the episodes.

Fourth, multiple studies have examined the relationship between inflammatory markers and major depression. Although most published studies found some increased inflammation in depressed patients, many exceptions have been reported [73, 75, 88]. The contradictory findings could be due to differences in case mix, especially related to the proportion of somatic depression in the study samples. This would also account for the ob-

servation that late-onset depression is associated with inflammation markers and atherosclerosis, whereas early-onset depression is not [89, 90].

Clinical Implications

The integrative model can reconcile some differences of opinion on screening and treatment of depression in ACS patients and help find and develop promising interventions for new randomized controlled trials. Some scholars discourage routine screening because there is little evidence that it produces better outcomes in CAD patients [1]. On the other hand, an advisory group from the American Heart Association Prevention Committee [116] proposed screening all post-ACS patients for depression at regular intervals during the post-ACS period, including during hospitalization, using a standardized depression symptom checklist. The debate has also led to different treatment suggestions. Some urge for aggressive standard treatment of depression in ACS patients [3, 114], while others advocate a more conservative approach [1] or a focus on interventions seeking to improve adherence to cardiac rehabilitation, stress management, and lifestyle changes [104].

Acknowledging the etiological heterogeneity and the negative health behavior effects of persistent depression may help resolve this debate. The model predicts that standard depression treatments will probably be ineffective for somatic depressions because of their atypical etiology and underlying neurophysiology. Standard depression treatments must lead to significant improvement in CAD risk factors in order to normalize atherosclerosis and CAD-associated abnormalities, including increased systemic inflammation, platelet activation (except selective serotonin reuptake inhibitors), endothelial dysfunction, reduced heart rate variability, and baroreceptor sensitivity [117]. If most depressions in ACS patients consist of the somatic type, screening seems problematic since somatic depression has no clearly effective treatment yet.

For persistent depression that is largely cognitive/affective, the model predicts that successful treatment might improve CAD prognosis via health behavior. With moderately effective treatments for cognitive/affective depression available [118, 119], screening may ultimately enhance the likelihood of successful treatment, provided that screening tools are not overinclusive and that effective treatment follows positive screening. Given the hypothesized tendency of post-ACS cognitive/affective depressions to improve spontaneously, it seems cost-effec-

tive to have a waiting period of 1 or 2 months to exclude spontaneous remissions or to start low-intensity psychosocial treatment (by a nurse practitioner for instance) in order to speed up 'spontaneous' remission.

If the depression is largely somatic, it seems more effective to directly target health behaviors and adherence to cardiac treatment, including cardiac rehabilitation and physical exercise. Those interventions may reduce cardiac risk factors and be the most effective strategy for improving long-term CAD and, indirectly, the somatic depression as well [106, 120], since its symptoms are fuelled by the CAD, underlying atherosclerosis, and associated physiological abnormalities. If these risk factors improve, the somatic symptoms may decrease in severity. Thus, aggressive treatment of cardiac risk factors such as poor lifestyle and physical inactivity may also be the best treatment currently available for somatic depression. Recent evidence suggests that exercise may be effective in treating both depression and CAD risk factors [107, 120]. If physical exercise and lifestyle interventions are effective for both somatic and cognitive/affective depression, they will be essential treatments in post-ACS depression as they would treat both the depression and help with the cardiac risk factors.

Future Directions

First, the core hypotheses of the model theory need further testing. To some extent, this can be achieved by (i) refining the measurement of depression (e.g., type, history, etiology, duration) [37, 119], (ii) documenting atherosclerosis and its progression, (iii) prospective research designs that carefully monitor depression and CAD outcomes, and (iv) including measures of plausible behav-

ioral (e.g., exercise) and physiological (e.g., inflammation markers) pathways through which the CAD effects of depression may be mediated. Such research will help pinpoint the cardiotoxic aspects of depression, the precise nature of the harmful CAD effects, and the mechanistic pathways that link depression to CAD progression. In addition, it is important to acknowledge the heterogeneity of depression [37, 119] and elucidate the characteristics of the depressions and patients that benefit from particular treatments [114]. This way depression type- and person-tailored interventions can be developed and evaluated.

Future research on the depression-CAD relationship will need to integrate psychological, behavioral, physiological, and neurobiological findings and to combine epidemiological, clinical, and experimental methods. What we have now are interesting pieces of a complicated jigsaw puzzle, but the pieces have yet to be assembled in a way that allows us to make progress beyond inconsistent findings and speculation and towards insights in causal processes and some measure of certainty. We hope the proposed integrative model will contribute to these goals.

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Disclosure Statement

Drs. Ormel and de Jonge report no conflict of interests.

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